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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HARALD GROEGER, ET AL.	EXAMINER: POPA
SERIAL NO: 10/593,567	:
FILED: AUGUST 21, 2007	ART UNIT: 1633
FOR: PROCESS FOR PREPARING OPTICALLY ACTIVE AMINO ACIDS USING A WHOLE-CELL CATALYST	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In accordance with 35 U.S.C. 134, that the claims of the present application have been twice rejected, this brief is submitted in response to the Final Office Action dated October 28, 2010 ("Final Action").

REAL PARTY OF INTEREST

The real party of interest is EVONIK DEGUSSA GMBH of ESSEN, GERMANY.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1-16 are active in this case.

Claims 1-16 are rejected and appealed. These claims are presented in Appendix I.

STATUS OF AMENDMENTS

No outstanding amendments are present in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the pending, rejected and appealed independent claim 1 with reference to exemplary support in the originally filed application.

A process for preparing enantiomerically enriched L-α-amino acids or their salts, comprising reacting the corresponding 2-ketocarboxylic acid with an ammonium ion donor in the presence of a whole-cell catalyst comprising a cloned gene encoding a cofactor-dependent amino acid dehydrogenase and a cloned gene encoding glucose dehydrogenase that regenerates the cofactor, at a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM and the external addition of cofactor, based on the total input of substrate, corresponds to < 0.0001 equivalents.

Page 5, line 18 to page 6, line 17 and page 7, lines 23-28.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(I) The first rejection to be reviewed on appeal is whether Claims 1-16 are properly rejected under 35 USC 103(a) in view of Galkin *et al*(Appl. Environ Microbiol, 1997, 63:4651-4656, "Galkin") in view of each of Yamamoto *et al* (U.S. PG PUB 2002/0064847, "Yamamoto"), Hong (Biotechnol Bioeng, 1986, 28:1421-1431, "Hong") and Smith *et al* (J Biol Chem, 1993, 268:10746-10753, "Smith") as set forth in the Final Action starting at page 7.

(II) The second rejection to be reviewed on appeal is whether Claims 1-16 are properly rejected, provisionally, under the doctrine of obviousness-type double patenting based on claims 1, 5-8 and 10-13 of co-pending application 12/205,371 in view of Hong as set forth in the Final Action at page 3.

(III) The third rejection to be reviewed on appeal is whether Claims 1-16 are properly rejected under the doctrine of obviousness-type double patenting based on Claims 1, 2 and 4-7 of U.S. patent no. 7,217,544 in view of Hong and Yamamoto as set forth in the Final Action at page 6.

ARGUMENT

The invention

As discussed on pages 5-6 of the present specification, the present invention provides another process for preparing L-α-amino acids which operates enzymatically and which can be carried out advantageously on an industrial scale. More specifically in a manner which is extremely elegant and surprising but nonetheless advantageous for that, by, in a process for preparing enantiomerically enriched L-α-amino acids or their salts by reacting the corresponding 2-ketocarboxylic acid with an ammonium ion donor in the presence of a whole-cell catalyst which comprises a cloned gene encoding a cofactor-dependent amino acid dehydrogenase and a cloned gene encoding an enzyme which regenerates the cofactor, defined as a glucose dehydrogenase, metering, at a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM and the external addition of cofactor, based on the total input of substrate, corresponds to < 0.0001 equivalents.

Surprisingly, it is possible, for example by using the whole-cell catalyst while at the same time metering in the substrate, to dispense with any addition of the expensive cofactor or, by means of making a minimal external addition (< 0.0001 equivalents), to keep its concentration in a low range, thereby providing advantages on process input costs. By contrast, without this metering technology and when initially introducing substrate quantities per reaction volumes of > 500 mM, the reductive amination using the whole-cell catalyst only succeeds when relatively large quantities of the NAD+ cofactor are added. In the absence of the latter, the concentration only proceeds unsatisfactorily (see comparative example "synthesis example 1", initial substrate quantity per reaction volumes 900 mM - final turnover 25%). It is consequently only by using the process according to the invention (see synthesis examples 2 to 5) that it is possible to be able to almost completely dispense with the

external addition of the cofactor even when carrying out the synthesis with relatively high total turnover quantities per reaction volumes and consequently under conditions which make sense from the point of process economics.

The first ground of rejection

The Examiner's rejection is set forth on pages 7-9 of the Final Action.

The Examiner finds that Galkin teaches a whole cell catalyst in a batch method to produce L-amino acids from ketocarboxylic acids in the presence of ammonium and does not explicitly state that a cofactor is added (see pp. 4652, col. 2, "Production of L and D amino acids").

The Examiner finds that Galkin does not teach a fed-batch process but as performing such a batch-fed process was known from, e.g., Hong, this aspect of the claimed invention would have been obvious.

The Examiner also concedes that Galkin does not teach glucose dehydrogenase but rather formate dehydrogenase for regenerating the cofactor. Thus, the Examiner cites to Yamamoto to allege that either formate dehydrogenase or glucose dehydrogenase can be used to regenerate NADH from NAD+ (see page 8, 2nd paragraph in the final Action and paragraph [0046] in Yamamoto) and therefore are equivalent.

Argument regarding the first rejection applied under 35 USC 103(a)

1. The first reversible error is the Examiner's use of hindsight to reconstruct the claims.

It is clear from the rejection that hindsight has been employed to reconstruct the claims from dipartite disclosures that have little to do with each other. To establish that Applicants' claimed process would have been obvious to a person having ordinary skill in the art, the prior art must reasonably suggest that persons having ordinary skill in the art do what Applicants claims require. Here, the only suggestion to do what Applicants have done is

Applicants' own disclosure, i.e. hindsight because the substrates, enzymes and products involved in the process disclosed in Galkin are completely different from the substrates, enzymes and products described in Hong and Yamamoto. In particular, Galkin teaches conversion of α-keto acids with *E. coli* cells with formate dehydrogenase whereas Yamamoto is relevant to a secondary alcohol dehydrogenase. Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

2. The second reversible error is the Examiner's failure to provide sufficient basis for the conclusions in the rejection

Even though it is acknowledged in the Action that Galkin nor any of the other citations in the rejection teach "a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM" in Claim 1, that is deemed to be obvious based on some unsupported theory of optimization. The examiner's statements in this regard are merely unsupported allegations that are not based on objective evidence or acceptable scientific reasoning. ([R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l.* v. *Teleflex Inc.*, 550 U.S. 398, 418 (2007)). See also *In re Lee,* 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (" 'The factual inquiry whether to combine references must be thorough and searching.'...It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.").

Further there are no teachings in the cited art that the substrate input should be more than 500 mM as claimed nor that this is a variable requiring optimization to the levels as claimed. The Examiner cannot properly conclude that those limitations would have been

obvious. See, .e.g., *In re Antonie*, 559 F.2d 618, 195 USPQ 6, 8-9 (CCPA 1977) (exceptions to rule that optimization of a result-effective variable is obvious, such as where the results of optimizing the variable are unexpectedly good or where the variable was not recognized to be result effective). See also *Ex parte Whalen*, 89 USPQ2d 1078 (Bd. Pat. App. & Int. 2008).

3. The third reversible error is the Examiner's reliance on Yamamoto's disclosure to assert equivalence of different enzymes

Further and with respect to the Examiner's contention that that formate dehydrogenase and glucose dehydrogenase are functional equivalents relying exclusively on Yamamoto in this regard, this position like so many in the rejection is simply unsubstantiated. Indeed, all that Yamamoto teaches is that each of those enzymes may be useful for regenerating NADH (see [0046] of Yamamoto) but nowhere in this paragraph nor anywhere else in Yamamoto's disclosure is there any statement that they are equivalent, particularly in a process for preparing enantiomerically enriched L-α-amino acids or their salts as claimed. Indeed, the Examiner's rejection is erroneous because "functional equivalence does not necessarily establish obviousness" (*In re Scott*, 323 F.2d 1016, 1019 (CCPA 1963) ("Expedients which are functionally equivalent to each other are not necessarily obvious in view of one another.") Absent evidence as to why one of ordinary skill would have replaced Galkin's explicit requirement for formate dehydrogenase based simply on the fact that formate dehydrogenase and glucose dehydrogenase may have similar utility is insufficient to render the claims *prima facie* obvious.

Presuming that the Board sides with the Examiner on this issue, the presentation of surprising results in the present specification rebuts that contention. "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be

enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987).

As demonstrated in the Examples of the present application, the use of a glucose dehydrogenase lead to a 97% conversion with a high enatioselectivity resulting from an amount of substrate of 0.9 M (see pp. 32, last paragraph of the specification). In contrast, Galkin teaches 0.3M achieved product. As so stated in the present specification, e.g., on page 5, that the Inventors achieved such a high conversion efficacy that can now be advantageously employed on an industrial scale was surprising and certainly not reasonably predictable from the combined teachings of the cited art.

4. The fourth reversible error is that Galkin teaches away from the present invention.

Contrary to the Examiner's contention, Galkin itself teaches away from those claim limitations. *In re Kahn* 441 F.3d 977, 985-86 (Fed. Cir. 2006): "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

This is so because the only example in Galkin where a substrate input of more than 500mM is used (Table 2, pyruvate 0.6M) resulted in a significant drop in efficiency (yield 75%) as compared to those examples where lower levels of the same substrate were used (yield = 95% for pyruvate = 0.2M and yield = 92% for pyruvate = 0.4M). Therefore, a person of skill in the art necessarily would take from Galkin's teaching that increasing the substrate concentration more than 0.4 M to be deleterious to the overall reaction. Therefore, even if the teachings of Galkin, Hong and Yamamoto were combined as suggested by the Examiner, a person of skill in the art would not have been motivated to combine the features

to arrive at the present invention as – in contrast to the requirements of present claim 1 – Galkin would have provided clear teachings to use substrate inputs of less than 0.4M.

A person of skill in the art starting from Galkin et al. would not have been motivated to modify the process disclosed therein at all, because the system disclosed is already a very complex system and without any indication of a chance to improve this system a person of skill would not have ventured to change that process with a reasonable expectation of success. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

The second and third grounds of rejections

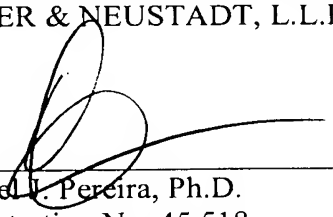
The provisional rejection citing co-pending application 12/205,371 and the rejection citing 7,217,544, each in view of Hong, are not sustainable as neither set of claims describes the inclusion of glucose dehydrogenase in the process that also requires a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM. For the reasons stated above in regard to the first ground of rejection, Hong's disclosure is insufficient to render obvious the claims as the alleged functional equivalence of the enzymes in question is unsupported and indeed fails to establish a reasonable expectation of success. Accordingly, the burden of establishing *prima facie* obviousness in these two rejections has not been met.

Conclusion

Appellants respectfully request that the Examiner's rejections be withdrawn with direction to allow all of the claims pending in this application and pass this case to issue.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.



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APPENDIX 1 (CLAIMS)

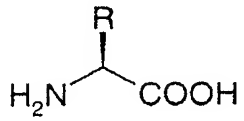
Claim 1 (Rejected) A process for preparing enantiomerically enriched L-α-amino acids or their salts, comprising reacting the corresponding 2-ketocarboxylic acid with an ammonium ion donor in the presence of a whole-cell catalyst comprising a cloned gene encoding a cofactor-dependent amino acid dehydrogenase and a cloned gene encoding glucose dehydrogenase that regenerates the cofactor, at a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM and the external addition of cofactor, based on the total input of substrate, corresponds to < 0.0001 equivalents.

Claim 2 (Rejected) The process as claimed in claim 1,

wherein no cofactor is added to the reaction mixture.

Claim 3 (Rejected) The process as claimed in claim 1,

wherein the 2 ketocarboxylic is one that will yield an amino acid of the general formula (I)



(I)

in which R is alkyl.

Claim 4 (Rejected) The process as claimed in claim 1, wherein the substrate is metered in accordance with a fed batch process.

Claim 5 (Rejected) The process as claimed in claim 1, wherein the 2-ketocarboxylic acid is kept at a maximum stationary concentration of less than 450 mM.

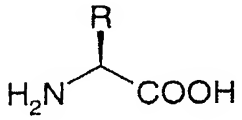
Claim 6 (Rejected) The process as claimed in claim 1, wherein before it is used, the whole-cell catalyst is pretreated such that the permeability of the cell membrane for the substrate and products is increased as compared with the intact system.

Claim 7 (Rejected) The process as claimed in claim 3, wherein R is a space-filling branched alkyl group that exhibits a tertiary C atom and possesses 5-10 carbon atoms.

Claim 8 (Rejected) The process as claimed in claim 7, wherein R is a tert-butyl or substituted alkyl.

Claim 9 (Rejected) The process as claimed in claim 5, wherein the 2-ketocarboxylic acid is kept at a maximum stationary concentration of less than 400 mM.

Claim 10 (Rejected) The process as claimed in claim 2, wherein the 2 ketocarboxylic is one that will yield an amino acid of the general formula (I)



(I)

in which R is alkyl.

Claim 11 (Rejected) The process as claimed in claim 2, wherein the substrate is metered in accordance with a fed batch process.

Claim 12 (Rejected) The process as claimed in claim 2, wherein the 2-ketocarboxylic acid is kept at a maximum stationary concentration of less than 450 mM.

Claim 13 (Rejected) The process as claimed in claim 2, wherein before it is used, the whole-cell catalyst is pretreated such that the permeability of the cell membrane for the substrate and products is increased as compared with the intact system.

Claim 14 (Rejected) The process as claimed in claim 10, wherein R is a space-filling branched alkyl group that exhibits a tertiary C atom and possesses 5-10 carbon atoms.

Claim 15 (Rejected) The process as claimed in claim 14, wherein R is a tert-butyl or substituted alkyl.

Claim 16 (Rejected) The process as claimed in claim 12, wherein the 2-ketocarboxylic acid is kept at a maximum stationary concentration of less than 400 mM.

APPENDIX II (EVIDENCE)

The present application as referenced within this brief.

APPENDIX III (RELATED APPEALS AND INTERFERENCES)

None.